

Oestrogen, brain function, and neuropsychiatric disorders

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Oestrogen has multiple effects on brain function

There is an increasing amount of research on the neurobiological effects of oestrogen. Also, health professionals are being asked for guidance on whether women should be prescribed oestrogen and progestogen hormone replacement therapy (HRT) not only to treat vasomotor instability and reduce bone loss, but also in various neuropsychiatric disorders. However, it is controversial whether oestrogen is indicated in the treatment of disorders such as depression, Alzheimer's disease, and schizophrenia. A recent large scale study examining the effects of HRT, funded by the National Institutes of Health (NIH) in the USA, was prematurely terminated owing to increased rates of breast cancer, heart disease, and stroke.¹ Shortly afterwards, the WISDOM trial funded by the MRC in the United Kingdom was also terminated. This has reinforced the need to have solid indications for the use of oestrogen-only replacement therapy.

OESTROGEN AS A NEUROPROTECTANT

Oestrogens affect the development and aging of brain regions that are crucial to higher cognitive functions (like memory) and are implicated in neuropsychiatric disorders such as Alzheimer's disease. For example, oestrogens increase synaptic and dendritic spine density in the hippocampus. In rats, oophorectomy results in a decrease in dendritic spine density in CA1 pyramidal cells, but this is prevented by the administration of oestrogens. Moreover, synaptic spine density is related to circulating oestradiol levels.² Until recently it was unclear how these oestrogen induced dendritic changes affected neuronal function. However, it has now been shown that oestrogen induces an increase in N-methyl-D-aspartate (NMDA) receptors in rat hippocampal neurones in the same region where an increase in dendritic spines is found, suggesting that the "new" oestrogen-induced spines are excitatory.^{3,4}

Among the most biologically plausible explanations why HRT might ameliorate age associated deficits in memory are modulatory effects on the cholinergic system in brain regions affected by

healthy aging and Alzheimer's disease (for example, the hippocampus and the association neocortex).⁵ The basal forebrain nuclei and hippocampus contain receptors for sex steroids.⁶ Further, in rats oestrogen reverses memory deficits, and ovariectomy decreases cholinergic uptake and choline acetyltransferase activity in the hippocampus and frontal cortex.^{7,8}

There are also indications that oestrogen affects central cholinergic function in healthy female humans. For example oestradiol modulates the growth hormone response to pyridostigmine throughout the menstrual cycle,⁹ and there is a significant correlation between oestradiol levels and cholinergic responsivity.¹⁰ We recently reported that cholinergic responsivity is greater in women who had received oestrogen replacement therapy than in those who had not.¹¹ Moreover, among long term users of oestrogen replacement therapy there was a positive correlation between enhanced cholinergic neurotransmission and longer duration of oestrogen exposure. In contrast, Smith *et al* found no significant between-group difference in density of the vesicular acetylcholine transporter located in presynaptic terminals (as measured using SPET and the radiotracer [¹²³I]BVM).¹² However, they did report a significant relation between length of HRT treatment and synaptic concentration in the frontal, temporal, and parietal cortices. That study was an important first step and suggests that although an overall effect of HRT was not found, it may influence the survival or plasticity of cholinergic cells. Taken together, these findings suggest that in older postmenopausal women oestrogen may be involved in the normal maintenance and physiological regulation of the cholinergic projections, and that oestrogen replacement can enhance the functional status of these cholinergic projections.

Various studies have addressed the relation between oestrogen and the serotonergic (5-hydroxytryptamine, 5-HT) system. The amygdala receives 5-HT projections from the raphe nuclei (at least in the rat)¹³ and oestrogen receptor α mRNA is abundantly expressed in the amygdala¹⁴ (oestrogen receptors occur in

two isoforms, α and β ; both subtypes are expressed in the brain, but with varying patterns of distribution—for a comprehensive review, see Hall *et al*¹⁵). In rats, the density of 5-HT_{2A} receptors increases during pro-oestrus in the frontal and cingulate cortex.¹⁶ Similarly, in ovariectomised rats there is an increase in central 5-HT₂ receptors but a decrease in 5-HT₁ receptors following oestrogen treatment.¹⁷ Thus oestrogen can modulate 5-HT receptor density and this may be of relevance to the action of antidepressants and atypical antipsychotics. Oestrogen also increases tryptophan hydroxylase mRNA levels in rhesus macaques¹⁸ and decreases monoamine oxidase activity in rat brain.⁶ Therefore oestrogen may both encourage the synthesis of 5-HT and decrease its catabolism. In humans, short term oestrogen replacement therapy increases 5-HT_{2A} receptor density, as measured by positron emission tomography (PET).¹⁹ Also, we showed that oestrogen replacement therapy modulates the age related reduction in serotonergic responsivity in healthy women.²⁰ Thus there is increasing evidence that oestrogen interacts with the 5-HT system at multiple levels and this may provide a theoretical role for oestrogen in the regulation of mood.

In addition to direct effects on neurones, oestrogens also act with neurotrophins to stimulate nerve cell growth indirectly. Oestrogen and neurotrophin receptors are co-expressed on rodent neurones in forebrain, hippocampus, and cerebral cortex, and this colocalisation may be important for neuronal survival.²¹ In addition, oestrogen can also protect against neurotoxins that boost free radical production,²² it can reduce the neuronal generation of β amyloid,²³ and it can act as an antioxidant.²⁴

In summary, there is increasing evidence that oestrogen modulates the aging of brain systems that are both crucial to higher cognitive function and implicated in mood and neuropsychiatric disorders such as Alzheimer's disease.

OESTROGEN AND COGNITIVE FUNCTION

The most robust effect of oestrogen on cognitive function is most probably on verbal memory. Prospective randomised studies of HRT versus placebo following total abdominal hysterectomy and bilateral salpingo-oophorectomy report a significant positive effect of estrogens on verbal memory.^{25,26} Performance in some cognitive tasks also varies as a function of the menstrual cycle in healthy premenopausal women. During the luteal phase (characterised by high levels of oestrogen and progesterone), verbal articulation is improved whereas spatial ability is decreased,²⁷ a pattern that is

reversed during the follicular phase (when there is relatively low oestrogen and progesterone). A similar pattern of cognitive performance is also observed if subjects are tested during the preovulatory oestradiol surge (to control for the potential effects of progesterone on cognitive performance), suggesting that oestrogen rather than progesterone is responsible for the observed cognitive effects.

Functional imaging techniques have also been employed to assess the effects of oestrogen on networks subserving various aspects of cognitive function (see Maki and Resnick²⁸ for a review). A recent randomised, placebo controlled crossover study using functional magnetic resonance imaging²⁹ found oestrogen induced alterations in brain activation patterns during encoding and retrieval of both verbal and non-verbal stimuli. More recently, Maki and Resnick³⁰ used PET and ¹⁵O to examine longitudinal changes in regional cerebral blood flow (rCBF) over a two year interval in women on and off HRT (both with and without adjuvant progesterone therapy). Significant differences in rCBF were found in the right hippocampus, the parahippocampal gyrus, and the left middle temporal gyrus—regions crucial to memory. We recently reported that oestrogen reduces age related differences in neuronal membrane breakdown (as measured by ¹H magnetic resonance spectroscopy) in the hippocampus and parietal lobe, and this was related to memory function.³¹

Thus there is increasing evidence from in vivo brain imaging studies that estrogen modulates cognitive function, cerebral blood flow, and membrane breakdown. However, further prospective randomised studies are required.

OESTROGEN AND ALZHEIMER'S DISEASE

Epidemiological studies have reported that the prevalence of Alzheimer's disease is significantly decreased in women on HRT, and that those women with Alzheimer's disease who were taking HRT had milder disease than those who were not.³² A recent longitudinal study reported that prolonged use of HRT decreased the risk and delayed the onset of Alzheimer's disease (relative risk = 0.40; 95% confidence interval, 0.22 to 0.85); moreover, the use of oestrogen for longer than one year reduced the risk of developing Alzheimer's disease by 5%.³³ However, results from such studies are often difficult to interpret. For example, women who use oestrogen are often better educated, generally healthier, and less depressed than non-users—a factor known as “the healthy user bias”. Thus we cannot exclude the possibility that

oestrogen use reflects an as yet unidentified bias that accounts for the effects observed.³³

Results from early clinical trials of HRT in people with Alzheimer's disease suggested that it may also benefit women with established disease. For example, women with Alzheimer's disease who were using oestrogen had better scores on the Alzheimer's disease assessment scale (ADAS-Cog, a standard instrument used in clinical trials on Alzheimer's disease) than their counterparts who did not take oestrogens.³⁴ However, results from recent large randomised double blind, placebo controlled trials are less optimistic.^{35–37} These studies reported no beneficial effects of HRT on cognition, mood, or functional outcomes in Alzheimer's disease. In contrast, a smaller study by Asthana *et al* reported a significant treatment benefit after a four week treatment period with oestradiol patches in subjects with Alzheimer's disease.³⁸ However, the effects were temporary and diminished once treatment ceased. The differences in results may be explained by differences in the type of HRT used (Asthana used an oestradiol patch, whereas Mulnard *et al* employed oral conjugated equine oestrogen (CEE) in 120 hysterectomised women with mild to moderate Alzheimer's disease for a period of one year³⁹). A significant improvement on the mini-mental state examination was also reported by Mulnard after two months' treatment with CEE. However, the benefit did not persist with prolonged treatment. Overall, oestrogen replacement therapy for one year did not slow disease progression or improve cognitive function.

Thus current evidence does not support a role for oestrogen in the treatment of established Alzheimer's disease. However, oestrogen may be a neuroprotectant in healthy brain and delay the onset of Alzheimer's disease. Perhaps in the established disease the potential therapeutic window has been missed and the remaining neurones are refractory to the beneficial effects of oestrogen, although oestrogen may still be useful as an augmentation strategy in those taking acetylcholinesterase inhibitors.⁴⁰

OESTROGEN AND SCHIZOPHRENIA

There are sex differences in premorbid functioning, age of onset, symptomatology, and outcome of schizophrenia. For example, men have a single peak of disease onset in their early twenties, whereas women have a later age of onset and a second peak in incidence between the ages of 45 and 55 years. In addition, women are more likely to have a family history of schizophrenia, display atypical

or affective features, and have a seasonal pattern of hospital admission. Because oestrogen has putative antidopaminergic/antipsychotic actions, it has been suggested that in women oestrogens may be responsible for the delayed onset of the first schizophrenia peak, and that the second peak may reflect the decline in oestrogen levels at the menopause. There is evidence that oestrogen protects the nigrostriatal dopaminergic system against the neurotoxic effects of MPTP in rats.^{41–43} An antipsychotic action of oestrogens is supported by clinical studies reporting that women have increased admission rates for psychosis around the menses⁴² and that psychotic symptomatology varies with phase of the menstrual cycle.^{43,44} Also, women with schizophrenia may have reduced oestradiol concentrations compared with controls.⁴⁴ However, there is currently little evidence to support the therapeutic use of oestrogen in schizophrenia. For example, when women with schizophrenia are treated with adjunctive oestrogen there is a slight increase in speed of recovery, but no improvement overall as compared with antipsychotic drug treatment alone.⁴⁵ Despite the lack of clear evidence for the efficacy of oestrogen as an antipsychotic agent, it remains plausible that oestrogen replacement therapy might protect against late onset schizophrenia in postmenopausal women by reducing age related changes in brain structure and neurochemistry (for example, in the hippocampus).

OESTROGEN AND DEPRESSION

Epidemiological studies suggest that, in addition to psychosocial factors, times of change in oestrogen levels make depression more likely in a vulnerable subgroup of women. For example, after puberty, women are around twice as likely to suffer depression than men⁴⁶ and in the postpartum period there is a peak of incidence.⁴⁷ However, although the perimenopausal period brings with it an increase in mild depressive symptoms, there is no increase in depressive disorders⁴⁶ and there is evidence that the prevalence of depression decreases postmenopausally.⁴⁸

In the light of the above findings, it has been suggested that oestrogen may have a role as an antidepressant. However, methodological difficulties affect the few studies in this area. These include small numbers of subjects, the lack of control groups, and (in the studies of menopausal depression) a variable or inadequate definition of the menopause and the use of multiple HRT preparations. In postpartum depression, oestrogen therapy may be useful both as prophylaxis in vulnerable individuals⁴⁹ and as a treatment.⁵⁰ In high doses,

oestrogen has been reported as being useful in non-postpartum treatment of resistant depression in women,⁵¹ but this small study has yet to be replicated. There is also some evidence that women taking oestrogen replacement therapy may respond better to fluoxetine.⁵² In the perimenopause, oestrogen replacement therapy is effective in reducing mild depressive symptoms⁴⁶ and it has been reported to be an effective treatment for depression.^{53–54} However, it is difficult to determine from these studies whether the oestrogen is treating menopausal symptoms such as sleep deprivation and anergia or the depression per se.

Currently, there is little evidence to suggest that oestrogen is a useful treatment for depression during the menopause or at other times. Indeed it is our opinion that oestrogen replacement or HRT should not be used as a first line treatment for depression in any group of depressed women, although in non-depressed individuals it can foster a sense of "psychological wellbeing" in the perimenopausal period.⁴⁶ Oestrogen may, however, have a role as a time limited (brief) adjunct to antidepressants in treatment resistant depression, or in the alleviation of mild mood symptoms (which are nonetheless distressing) in peri-postmenopausal women.

CONCLUSIONS

Basic research indicates that oestrogen has multiple effects on brain function, modulating aspects of neurotransmitter function, glucose metabolism, synaptogenesis, and brain aging. In line with this, epidemiological studies implicate oestrogen in the aetiology of neuropsychiatric disorders. However, these encouraging findings do not at present translate into the use of oestrogen as a treatment. Current evidence suggests that oestrogen alone has no role in the treatment of established Alzheimer's disease, but may delay its onset. The evidence base for the use of oestrogen as an adjunct to neuroleptics in schizophrenia or in the treatment of postnatal and perimenopausal depression is currently too weak to merit a change in clinical practice. Larger prospective studies are required to establish whether oestrogen has a role in the prophylaxis and treatment of these disorders.

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REFERENCES

- 1 Writing group for the Women's Health Initiative. Risks and benefits of oestrogen plus progestin in healthy postmenopausal women. *JAMA* 2002;288:321–33.
- 2 Gould E, Woolley CS, Frankfurt M, et al. Gonadal steroids regulate dendritic spine density in hippocampal pyramidal cells in adulthood. *J Neurosci* 1990;10:1286–91.
- 3 Gazzaley AH, Weiland NG, McEwen BS, et al. Differential regulations of NMDAR1 mRNA and protein by estradiol in the rat hippocampus. *J Neurosci* 1996;16:6830–8.
- 4 Woolley CS, Weiland NG, McEwen BS, et al. Estradiol increases the sensitivity of hippocampal CA1 pyramidal cells to NMDA receptor-mediated synaptic input: correlation with dendritic spine density. *J Neurosci* 1997;17:1848–59.
- 5 McEwen BS, Alves SE, Bulloch K, et al. Ovarian steroids and the brain: implications for cognition and aging. *Neurology* 1997;48(suppl 7):S8–15.
- 6 Luine VN, Khychevskaya RI, McEwen BS. Effect of gonadal steroids on activities of monoamine oxidase and choline acetylase in rat brain. *Brain Res* 1975;86:293–306.
- 7 Singh M, Meyer EM, Millard WJ, et al. Ovarian steroid deprivation results in a reversible learning impairment and compromised cholinergic function in female Sprague-Dawley rats. *Brain Res* 1994;644:305–12.
- 8 Gibbs RB, Burke AM, Johnson DA. Estrogen replacement attenuates effects of scopolamine and lorazepam on memory acquisition and retention. *Hormones Behav* 1998;34:112–25.
- 9 O'Keane V, Dinan TG. Sex steroid priming effects on growth hormone response to pyridostigmine throughout the menstrual cycle. *J Clin Endocrinol Metab* 1992;75:11–14.
- 10 Lucey JV, O'Keane V, O'Flynn K, et al. Gender and age differences in the growth hormone response to pyridostigmine. *Int Clin Psychopharmacol* 1991;6:105–9.
- 11 Van Amelsvoort T, Murphy DGM, Robertson D, et al. Effects of long-term estrogen replacement therapy on growth hormone response to pyridostigmine in healthy postmenopausal women. *Psychoneuroendocrinology* 2003;28:101–12.
- 12 Smith YR, Minoshima S, Kuhl DE, et al. Effects of long-term hormone therapy on cholinergic synaptic concentrations in healthy postmenopausal women. *J Clin Endocrinol Metab* 2001;86:679–84.
- 13 Vertes RP. A PHAL analysis of ascending projections of the dorsal raphe nucleus in the rat. *J Comp Neurol* 1991;313:643–68.
- 14 Osterlund MK, Keller E, Hurd YL. The human forebrain has discrete estrogen receptor alpha messenger RNA expression: high levels in the amygdaloid complex. *Neuroscience* 2000;95:333–42.
- 15 Hall JM, Couse JF, Korach KS. The multifaceted mechanisms of estradiol and estrogen receptor signaling. *J Biol Chem* 2001;276:36869–72.
- 16 Sumner BE, Fink G. The density of 5-hydroxytryptamine 2A receptors in forebrain is increased at pro-oestrus in intact female rats. *Neurosci Lett* 1997;234:7–10.
- 17 Biegon A, Reches A, Snyder L, et al. Serotonergic and noradrenergic receptors in the rat brain: modulation by chronic exposure to ovarian hormones. *Life Sci* 1983;32:2015–21.
- 18 Pecins-Thompson M, Brown NA, Kohama SG, et al. Ovarian steroid regulation of tryptophan hydroxylase mRNA expression in rhesus macaques. *J Neurosci* 1996;16:7021–9.
- 19 Moses EL, Drevets WC, Smith G, et al. Effects of estradiol and progesterone administration on human serotonin 2A receptor binding: a PET study. *Biol Psychiatry* 2000;48:854–60.
- 20 van Amelsvoort T, Abel KM, Robertson DM, et al. Prolactin response to d-fenfluramine in postmenopausal women on and off ERT: comparison with young women. *Psychoneuroendocrinology* 2001;26:493–502.
- 21 Toran-Allerand CD. The estrogen/neurotrophin connection during neural development: is co-localization of estrogen receptor with the neurotrophins and their receptors biologically relevant? *Dev Neurosci* 1996;18:36.
- 22 Simpkins JW, Singh M, Bishop J. The potential role for estrogen replacement therapy in the treatment of the cognitive decline and neurodegeneration associated with Alzheimer's disease. *Neurobiol Aging* 1994;15(suppl 2):S195–7.
- 23 Xu H, Gouras GK, Greenfield JP, et al. Estrogen reduces neuronal generation of Alzheimer beta-amyloid peptides. *Nat Med* 1998;4:447–51.
- 24 Behl C. Oestrogen as a neuroprotective hormone. *Nat Rev Neurosci* 2002;3:433–42.
- 25 Sherwin BB. Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. *Psychoneuroendocrinology* 1988;13:345–57.
- 26 Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. *Psychoneuroendocrinology* 1992;17:485–95.
- 27 Hampson E. Variations in sex-related cognitive abilities across the menstrual cycle. *Brain Cogn* 1990;14:26–43.
- 28 Maki PM, Resnick SM. Effects of estrogen on patterns of brain activity at rest and during cognitive activity: a review of neuroimaging studies. *Neuroimage* 2001;14:789–801.
- 29 Shaywitz SE, Shaywitz BA, Pugh KR, et al. Effect of estrogen on brain activation patterns in postmenopausal women during working memory tasks. *JAMA* 1999;281:1197–202.
- 30 Maki PM, Resnick SM. Longitudinal effects of estrogen replacement therapy on PET cerebral blood flow and cognition. *Neurobiol Aging* 2000;21:373–83.
- 31 Robertson DM, van Amelsvoort T, Daly E, et al. Effects of estrogen replacement therapy on human brain aging: an in vivo 1H MRS study. *Neurology* 2001;57:2114–17.
- 32 Henderson VW, Paganini-Hill A, Emanuel CK, et al. Estrogen replacement therapy in older women: comparisons between Alzheimer's disease cases and nondemented control subjects. *Arch Neurol* 1994;51:896–900.
- 33 Tang MX, Jacobs D, Stern Y, et al. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet* 1996;348:429–32.
- 34 Doraiswamy PM, Krishen A, Martin WL, et al. Gender, concurrent estrogen use and cognition in Alzheimer's disease. *Int J Geriatr Psychopharmacol* 1997;1:34–7.
- 35 Wang PN, Liao SQ, Liu RS, et al. Effects of estrogen on cognition, mood, and cerebral blood flow in AD: a controlled study. *Neurology* 2000;54:2061–6.
- 36 Henderson VW, Paganini-Hill A, Miller BL, et al. Estrogen for Alzheimer's disease in women: randomized, double-blind, placebo-controlled trial. *Neurology* 2000;54:295–301.
- 37 Mulnard RA, Cotman CW, Kawas C, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study. *JAMA* 2000;283:1007–15.
- 38 Asthana S, Baker LD, Craft S, et al. High-dose estradiol improves cognition for women with AD: results of a randomized study. *Neurology* 2001;57:605–12.
- 39 Mulnard RA, Cotman CW, Kawas C, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. *JAMA* 2000;283:1007–15.
- 40 Schneider LS, Farlow MR, Henderson VW, et al. Effects of estrogen replacement therapy on response to tacrine in patients with Alzheimer's disease. *Neurology* 1996;46:1580–4.
- 41 Diuzen DE, McDermott JL, Liu B. Estrogen alters MPTP-induced neurotoxicity in female mice: effects on striatal dopamine concentrations and release. *J Neurochem* 1996;66:658–66.

- 42 **Hallonquist JD**, Seeman MV, Lang M, *et al*. Variation in symptom severity over the menstrual cycle of schizophrenics. *Biol Psychiatry* 1993;**33**:207–9.
- 43 **Lindamer LA**, Lohr JB, Harris MJ, *et al*. Gender, estrogen, and schizophrenia. *Psychopharmacol Bull* 1997;**33**:221–8.
- 44 **Riecher-Rossler A**, Hafner H, Dutsch-Strobel A, *et al*. Further evidence for a specific role of estradiol in schizophrenia? *Biol Psychiatry* 1994;**36**:492–4.
- 45 **Kulkarni J**, Riedel A, de Castella AR, *et al*. Estrogen – a potential treatment for schizophrenia. *Schizophr Res* 2001;**48**:137–44.
- 46 **Epperson CN**, Wisner KL, Yamamoto B. Gonadal steroids in the treatment of mood disorders. *Psychosom Med* 1999;**61**:676–97.
- 47 **Kumar R**, Robson KM. A prospective study of emotional disorders in childbearing women. *Br J Psychiatry* 1984;**144**:35–47.
- 48 **Bebbington PE**, Dunn G, Jenkins R, *et al*. The influence of age and sex on the prevalence of depressive conditions: report from the National Survey of Psychiatric Morbidity. *Psychol Med* 1998;**28**:9–19.
- 49 **Sichel DA**, Cohen LS, Robertson LM, *et al*. Prophylactic estrogen in recurrent postpartum affective disorder. *Biol Psychiatry* 1995;**38**:814–18.
- 50 **Gregoire AJ**, Kumar R, Everitt B, *et al*. Transdermal oestrogen for treatment of severe postnatal depression. *Lancet* 1996;**347**:930–3.
- 51 **Klaiber EL**, Broverman DM, Vogel W, *et al*. Estrogen therapy for severe persistent depressions in women. *Arch Gen Psychiatry* 1979;**36**:550–4.
- 52 **Schneider LS**, Small GW, Hamilton SH, *et al*. Estrogen replacement and response to fluoxetine in a multicenter geriatric depression trial. Fluoxetine Collaborative Study Group. *Am J Geriatr Psychiatry* 1997;**5**:97–106.
- 53 **Schmidt PJ**, Nieman L, Danaceau MA, *et al*. Estrogen replacement in perimenopause-related depression: a preliminary report. *Am J Obstet Gynecol* 2000;**183**:414–20.
- 54 **Soares CN**, Almeida OP, Joffe H, *et al*. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2001;**58**:529–34.

Acute stroke

Clinical radiologic correlations in acute stroke: is the signal intensity at the end of the tunnel getting brighter quicker?

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Is time to clot lysis the key factor predicting outcome after focal cerebral ischaemia?

Current practice relies on time dependent criteria for decisions regarding acute stroke therapy. This is based on the results of the NINDS rt-PA Stroke Trial,^{1,2} animal,³ and other clinical studies⁴ that indicate that time to clot lysis is the key factor predicting outcome after focal cerebral ischaemia. We know that every patient at the same time from symptom onset of ischaemic stroke does not benefit equally from acute therapies. Factors other than time, such as collateral circulation, stroke aetiology, permanent versus intermittent occlusive process, coagulation state, age, underlying disease state (eg diabetes mellitus, hypertension, haematocrit), sex, and other genetic factors, are likely to influence response to thrombolysis and other acute therapies.⁵ Current investigations are seeking alternate protocols, biological markers, and criteria for acute therapy, some of which are based on imaging of the purported ischaemic core and penumbra.⁶ The study by Adler *et al*⁷ (pp 886–888, this issue) looks to enhance our ability to go beyond strictly time based criteria for acute stroke therapies. These investigators examined the utility of standard clinical assessments (NIH Stroke Scale and the Oxfordshire Community Stroke Project) in conjunction

with MRI studies. Using the clinical assessment scale, they demonstrated a consistent ability to predict which patients were more likely to have a large diffusion weighted imaging (DWI-PWI) mismatch and persisting cerebral arterial occlusion. The results of this study fit well with the study by Barber *et al*, who demonstrated that absent MCA flow on MRA predicted a DWI-PWI mismatch, and, therefore, possibly the ischaemic penumbra.⁸

Use of advanced clinical imaging technology, such as MRI DWI-PWI and MRA, has been a significant step forward in the assessment of brain injury in acute stroke, and we need to remain on firm ground to ensure continued progress. As suggested by other authors, this study assumes that “areas of high signal intensity on DWI were taken to be indicative of irreversible cerebral infarction”, and therefore not salvageable.^{8–9} Is this a safe/accurate assumption?

There appears to be three potential fates for areas of tissue with high signal intensity on DWI: (a) irreversible injury, (b) reversible injury, and (c) late injury. In a small series of patients, Kidwell and colleagues reported reversal of DWI

signal abnormalities after intra-arterial thrombolysis, which correlated to improved clinical outcome in several cases.¹⁰ Animal studies in models of ischaemia and reperfusion have shown the delayed recurrence of DWI lesions after initial normalisation, which correlated to histologic indicators of neuronal damage.¹¹ DWI is a composite of the apparent diffusion coefficient (ADC) and T2 weighting. Pseudo-normalisation of DWI may be an artifact of the varying impact of these two components.¹¹ ADC values in rats after middle cerebral artery occlusion and reperfusion have also been shown to normalise and secondarily become abnormal with underlying histologic evidence of ischaemic damage, but with no worse functional outcome (similar to the fate of the human subjects in the initial Kidwell study).¹² Subsequently Kidwell's group showed MRI confirmation of these basic studies with the DWI abnormalities either remaining, normalising, or secondarily becoming abnormal.¹³ Further studies delineating the significance of MRI and molecular changes following ischaemia, and what clinical impact these changes have, will lead to a greater understanding of their significance and potentially new criteria to determine best stroke therapy.

As these new MR techniques are being applied to acute stroke, the very definition of TIA is again under fire. In this study, the authors rely on a clinical definition of stroke when it was at odds with the DWI evidence for cerebral injury. Others have suggested a new definition of TIA that would take into account all information available, including advanced imaging methods, and exclude episodes that had evidence for ischaemic injury and refer to them as a stroke.¹⁴

By showing a method that may reliably predict a diffusion/perfusion mismatch in a subset of patients, the authors have helped us on our progress